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The emerging roles of ARID1A in tumor suppression

Ren-Chin Wu[1,2], Tian-Li Wang[1,3], and Ie-Ming Shih[1,3,*]

[1]Department of Pathology and Pathobiology Graduate Program; Johns Hopkins University School of Medicine; Baltimore, MD USA; [2]Department of Pathology; Chang Gung Memorial Hospital and Chang Gung University College of Medicine; Taoyuan, Taiwan; [3]Departments of Oncology and Gynecology and Obstetrics; Johns Hopkins University School of Medicine; Baltimore, MD USA

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ARID1A has emerged as a tumor suppressor gene, which is mutated in a broad spectrum of cancers, especially in those arising from ectopic or eutopic endometrium. As a subunit of SWI/SNF chromatin remodeler, ARID1A facilitates target-specific binding of SWI/SNF complexes to chromatin, thereby altering the accessibility of chromatin to a variety of nuclear factors. In human cancer, ARID1A possesses not only features of a gatekeeper, regulating cell cycle progression, but also features of a caretaker, preventing genomic instability. An increasing body of evidence suggests crosstalk between ARID1A and PI3K/Akt pathways, and between ARID1A and p53. In this review, we discuss the spectrum of ARID1A alterations in cancers, tumor suppression mechanisms of ARID1A, oncogenic pathways cooperating with ARID1A, and clinical implications of *ARID1A* mutation.

Introduction

Dysregulation of ATP-dependent chromatin remodeling complexes has been implicated in a variety of cancers in an increasing number of studies.[1,2] These complexes utilize the energy of ATP hydroxylation to reposition, eject, or exchange nucleosomes, thereby modulating DNA accessibility to other cellular machineries involved in transcription, DNA replication, methylation, and repair.[3] Among different ATP-dependent chromatin remodelers, SWitch/Sucrose NonFermentable (SWI/SNF) is the most commonly dysregulated in cancer, and *ARID1A* (*AT-rich interactive domain-containing protein 1A*) is the most frequently mutated among all genes encoding subunits of SWI/SNF complexes.[4]

Recently, *ARID1A* has been established as a tumor suppressor gene through the discovery of recurrent inactivating *ARID1A* mutations in a broad spectrum of cancers, and its tumor suppressor role has been supported by functional studies. In this review, we discuss the spectrum of ARID1A alterations in cancers, known biological functions of ARID1A, the possible mechanism how ARID1A suppresses tumor development, and the potential of using ARID1A as a prognostic biomarker.

*Correspondence to: Ie-Ming Shih; Email: ishih@jhmi.edu
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ARID1A is a Subunit of SWI/SNF Chromatin Remodeler

ARID1A, also known as BAF250a, SMARCF1, or p270, belongs to a family of proteins containing a highly conserved, approximately 100-amino acid DNA binding domain called ARID (AT-rich interacting domain). Although the ARID domains in general preferentially bind AT-rich DNA sequences, the ARID domain of mammalian ARID1A exhibits general DNA binding character without sequence specificity.[5,6] The C-terminal domain of ARID1A, presumably important for protein–protein interaction, contains multiple copies of the sequence motif, LXXLL, which has been shown to facilitate the interaction of various proteins with nuclear hormone receptors.[7]

ARID1A, as well as its paralog ARID1B, associates in a mutually exclusive fashion with several other proteins to form the BRG1-associated factor (BAF) complexes, a subfamily of mammalian SWI/SNF chromatin remodelers. BAF complexes are composed of one of two mutually exclusive ATPase subunits (BRM and BRG1), a set of core subunits (BAF47, BAF155, and BAF170) that augment catalytic activity, and variant subunits that were thought to provide target specificity.[8] Mammalian SWI/SNF complexes are essential in regulating gene expression, and have been implicated in several cellular functions, including proliferation, cell fate determination, self-renewal in stem cells, DNA methylation, and damage repair.[1,8-10] Like ARID1A, several subunits of SWI/SNF complexes have multiple paralogs, making it possible to form hundreds of different SWI/SNF complex combinations by incorporating different paralogous subunits.[11] This combinatorial assembly of SWI/SNF complexes is thought to provide the target and lineage specificity exhibited by different forms of SWI/SNF complexes.[12] Indeed, distribution of ARID1A and ARID1B varies in mouse embryonic tissues, and they demonstrate different kinetic patterns during cell cycle progression; ARID1A accumulates in G_0/G_1 phase and is downregulated in S and G_2/M phases, whereas ARID1B expression remains constant throughout all phases.[13] Therefore, differential incorporation of ARID1 proteins is likely responsible for directing BAF complexes to various targets, thus contributing to cell cycle regulation in different biological contexts.[14]

It is thought that ARID1A contributes to targeting of BAF complexes in two ways. First, ARID1A may mediate recruitment

of BAF complexes to target DNA regulatory elements through interacting with other transcription (co-)factors. ARID1A has been shown to interact with ligand-bound nuclear hormone receptors and p53 through its C-terminal domain and stimulate transcriptional activity of these transcription factors.[15-17] Second, the ARID domain, despite showing no sequence specificity in vitro, may be crucial for improving BAF affinity to chromatin for certain targets in vivo. Chandler et al. demonstrated that ARID–DNA interactions contribute to SWI/SNF activity in mouse embryos in which missense mutation of the ARID domain disrupted ARID1A–DNA interactions. This results in a decrease in promoter occupancy by SWI/SNF, and defects in cardiovascular development.[18] Since missense mutations involving the ARID domain are present in human cancers, it raises a possibility that ARID–DNA interactions are essential for the tumor suppressor function of ARID1A and loss of such interaction (due to mutations) abolishes its tumor suppression function.

ARID1A acts as a nucleocytoplasmic protein whose stability depends on its subcellular localization. Nuclear ARID1A is less stable than cytoplasmic ARID1A because the protein is rapidly degraded by the ubiquitin–proteasome system present in the nucleus.[19] A naturally occurring in-frame deletion that disrupts the consensus nuclear export signal results in reduced steady-state protein levels of ARID1A due to its retention in the nuclei and subsequent degradation.[19] These findings delineate the basic biological mechanism regulating ARID1A subcellular distribution and protein stability.

ARID1A Mutations in Human Cancers

The *ARID1A* gene maps to chromosome 1p36.11, a region frequently deleted in cancer.[20] Initial clues that ARID1A was a tumor suppressor came from expression analyses that showed decreased ARID1A expression in 30% of renal cancer and 10% of breast cancer,[21] as well as discovery of *ARID1A* deletions and rearrangement in a few cancer cell lines.[22] Not until the advent of next-generation sequencing did the first concrete evidence that *ARID1A* was a tumor suppressor gene emerge. Two genome-wide sequencing studies in 2010 discovered frequent loss-of-function somatic mutations in endometriosis-associated ovarian cancers, including ovarian clear cell carcinoma and ovarian endometrioid carcinoma, which harbored *ARID1A* somatic mutation in 46–57% and 30%, respectively.[23,24] Subsequent comprehensive sequencing efforts have reported frequent somatic mutations in *ARID1A* in other types of cancers in addition to endometriosis-associated neoplasms (**Table 1**), including uterine endometrioid carcinoma (39~44%),[30-32] gastric carcinoma (8~29%),[20,43-45] esophageal adenocarcinoma (9~19%),[21,40-42] Waldenstrom macroglobulinemia (17%),[22,63] pediatric Burkitt lymphoma (17%),[23,62,67] hepatocellular carcinoma (10~16%),[48-50,67] cholangiocarcinoma (14~15%),[32,51,52] and urothelial carcinoma of bladder (12~15%).[57-59] These mutations, most of which are deletion or nonsense mutations, are distributed throughout the *ARID1A* gene. **Figure 1** summarizes their mutation frequencies in reported human neoplastic diseases. In addition, studies applying immunohistochemistry have also identified frequent loss of ARID1A expression in several additional tumor types (**Table 1**) including ovarian endocervical-type mucinous borderline tumor (33%),[29] cervical adenocarcinoma (24~31%),[38] endometrial clear cell carcinoma (21~26%),[33,35-37] endometrial carcinosarcoma (14%),[33] and anaplastic thyroid carcinoma (14%).[33] Comparative genomic hybridization studies have also detected frequent heterozygous deletions involving *ARID1A* in pancreatic cancer (36~47%),[53,68] breast cancer (13~35%),[55,69] and clear cell renal cell carcinoma (16%).[70] Overall, the frequency and pattern of *ARID1A* mutations indicates that ARID1A is altered in a broad spectrum of human cancers.

ARID1A Mutations in Precancerous Lesions

Loss of ARID1A protein expression is a surrogate marker for ARID1A loss of function mutations,[24] and immunohistochemistry has been used to study ARID1A expression in tumor precursor lesions of which the small size challenges direct sequence analysis. Loss of ARID1A appears to be an early molecular event in developing ovarian and endometrial cancers. Yamamoto et al. showed a strikingly high prevalence of ARID1A loss in the precursor lesions adjacent to ovarian clear cell carcinomas, including 86% of non-atypical and 100% of atypical endometriosis and clear-cell adenofibroma components.[71] In a study by Ayhan et al., all 31 ARID1A-negative ovarian carcinomas arising in ovarian endometriotic cysts lost ARID1A expression in the contiguous endometriotic cyst epithelium.[72] In contrast, ARID1A loss is rarely found in endometriosis not associated with cancerous tissue, or in precursor lesions of ARID1A-expressing cancers.[71,72] In endometrial cancer, Werner et al. found frequent ARID1A loss (16%) in complex endometrial hyperplasia with atypia, the precursor lesion of uterine endometrioid carcinoma.[35] Similarly, Mao et al. reported that the percentage of complete ARID1A loss increased from 0% in complex atypical hyperplasia, to 25% in low-grade endometrioid carcinoma, to 44% in high-grade endometrioid carcinoma.[73] These findings suggest that loss of ARID1A expression, presumably due to mutation, plays an important role in tumor progression of uterine endometrioid carcinoma. In addition to gynecologic cancers, ARID1A protein loss was also identified in Barrett esophagus, a precancerous lesion of esophageal adenocarcinoma, and frequency of loss was higher in lesions with more severe dysplasia.[41] The occurrence of *ARID1A* mutations in these precancerous lesions suggests an important role for ARID1A inactivation in tumor initiation.

Mechanisms of Tumor Suppression: Gatekeeper or Caretaker?

Tumor suppressor genes can be broadly grouped into two classes—"caretakers" and "gatekeepers".[74] Gatekeepers control cellular proliferation, usually through regulating cell cycle or promoting apoptosis, whereas caretakers maintain the integrity of the genome. Functional studies of ARID1A have shown that

Table 1. Recurrent mutation and protein loss of ARID1A in cancers[a]

Cancer types	Mutation (%)	Protein loss (%)	References
Ovarian clear cell carcinoma	24/42 (57%)	N/A	23
	55/119 (46%)	55/132 (42%)	24
	N/A	88/149 (59%)	25
	N/A	35/68 (52%)	26
	N/A	40/90 (44%)	27
	N/A	34/82 (41%)	28
Ovarian endometrioid carcinoma	10/33 (30%)	39/125 (31%)	24
	N/A	62/130 (48%)	28
Ovarian endocervical-type mucinous borderline tumor	N/A	8/24 (33%)	29
Endometrial endometrioid carcinoma	82/186 (44%)	N/A	30
	10/25 (40%)	15/58 (26%)	31
	73/186 (39%)	N/A	32
	N/A	73/214 (34%)	33
	N/A	27/111 (24%)	34
	N/A	84/436 (19%)	35
Endometrial serous carcinoma	4/42 (10%)	N/A	32
	N/A	17/95 (18%)	33
	N/A	1/44 (3%)	35
	N/A	0/17 (0%)	31
Endometrial clear cell carcinoma	N/A	6/23 (26%)	33
	N/A	5/22 (23%)	36
	N/A	4/19 (21%)	35
	N/A	10/50 (20%)	37
Endometrial carcinosarcoma	N/A	18/127 (14%)	33
Cervical adenocarcinoma	N/A	14/45 (31%)	38
	N/A	6/25 (24%)	39
Cervical squamous cell carcinoma	N/A	19/116 (16%)	39
	N/A	3/46 (7%)	38
Esophageal adenocarcinoma	10/54 (19%)	N/A	40
	3/20 (15%)	12/98 (12%)	41
	14/149 (9%)	N/A	42
Gastric carcinoma	32/109 (29%)	22/109 (20%)	43
	10/100 (10%)	N/A	44
	9/110 (8%)	N/A	45
	N/A	26/180 (14%)	33
	N/A	5/45 (11%)	31
	N/A	94/857 (11%)	46
Colorectal carcinoma	12/119 (10%)	N/A	44
	21/224 (9%)	N/A	47
	N/A	2/49 (4%)	31
	N/A	2/250 (1%)	33

[a]Only cancer types with >5% mutation or protein loss were shown. [b]Less stringent criteria were used for IHC interpretation.

Table 1. Recurrent mutation and protein loss of ARID1A in cancers[a] (continued)

Cancer types	Mutation (%)	Protein loss (%)	References
Hepatocellular carcinoma	20/125 (16%)	N/A	48
	14/110 (13%)	N/A	49
	15/147 (10%)	N/A	50
	N/A	0/41 (0%)	31
Cholangiocarcinoma	32/209 (15%)	N/A	51
	9/64 (14%)	N/A	52
	N/A	2/27 (7%)	31
Pancreatic adenocarcinoma	10/119 (8%)	N/A	44
	3/36 (8%)	N/A	53
Breast carcinoma	4/114 (4%)	N/A	44
	11/507 (2%)	N/A	54
	0/11 (0%)	64% (n = 236)[b]	55
	N/A	63/112 (56%)[b]	56
	N/A	11/315 (3%)	33
	N/A	1/91 (1%)	31
Urothelial carcinoma of bladder	15/99 (15%)	N/A	57
	13/97 (13%)	N/A	58
	6/52 (12%)	N/A	59
Anaplastic thyroid carcinoma	N/A	5/35 (14%)	33
Cutaneous melanoma	14/121 (12%)	N/A	60
	3/25 (12%)	N/A	61
Pediatric Burkitt lymphoma	5/29 (17%)	N/A	62
Waldenstrom macroglobulinemia	5/30 (17%)	N/A	63
Lung adenocarcinoma	15/183 (8%)	N/A	64
Lung squamous cell carcinoma	12/178 (7%)	N/A	65
Neuroblastoma	4/71 (6%)	N/A	66

[a]Only cancer types with >5% mutation or protein loss were shown. [b]Less stringent criteria were used for IHC interpretation.

it is a tumor suppressor with functions related to both gatekeepers and caretakers in different model systems. Thus, inactivating ARID1A through somatic mutations and other epigenetic mechanisms results in loss of both gatekeeper and caretaker functions in cells, thus promoting tumor initiation.

ARID1A as a Gatekeeper

ARID1A has been demonstrated to be capable of repressing cellular proliferation in a variety of cancers. For endometriosis-associated gynecologic cancers, restoration of ARID1A expression suppressed both in vitro cellular proliferation and tumor xenograft growth in an ovarian clear cell carcinoma cell line and a uterine endometrioid carcinoma cell line; whereas, silencing ARID1A expression in cell lines derived from normal ovarian surface epithelium increased the rate of cellular proliferation.[17] In breast cancer, ARID1A restoration inhibited proliferation in culture and growth in soft agar of *ARID1A*-mutated, T47D cells, whereas silencing ARID1A in *ARID1A* wild-type MCF-7 cells led to increased proliferation.[55] In gastric cancer, knockdown of wild-type ARID1A in four gastric cancer cell lines enhanced proliferation, whereas restoring ARID1A expression suppressed tumor proliferation in three *ARID1A*-deleted gastric cancer cell lines.[45,75] In bile duct cancer, silencing of ARID1A in three cell lines with wild-type *ARID1A* resulted in increased proliferation, which was reversed when ARID1A was re-expressed ectopically.[51] In hepatocellular carcinoma, ARID1A knockdown significantly promoted cellular proliferation of four wild-type cell lines but did not affect a cell line with *ARID1A* mutation.[49] The results of these functional studies indicate that *ARID1A* functions as a gatekeeper tumor suppressor gene.

As a gatekeeper, ARID1A regulates cell cycle entry and progression. In an MC3T3-E1 pre-osteoblast cell line model, ARID1A-depleted cells failed to undergo differentiation-associated cell cycle arrest upon induction with ascorbic acid, a differentiation

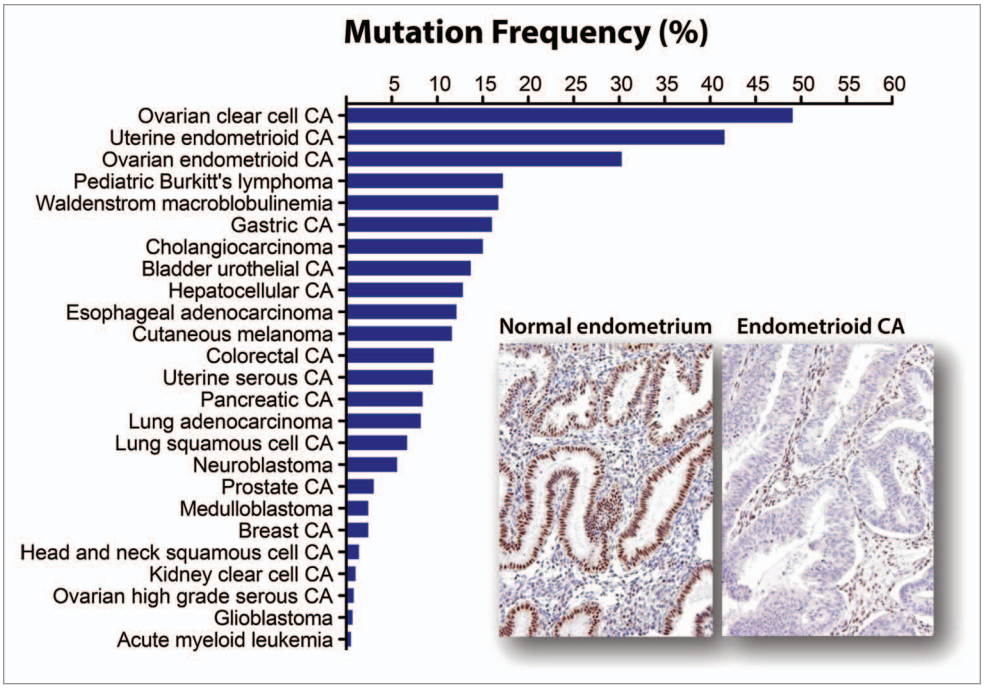

Figure 1. Mutation frequency of *ARID1A* among human cancers. A total of 594 mutated samples from 5160 tumors belonging to 25 different tumor types have been reported (as of January 2014). Among all neoplastic diseases analyzed, *ARID1A* mutation is most prevalent in ovarian clear cell carcinoma, uterine endometrioid carcinoma, and ovarian endometrioid carcinoma, all of which are derived from either ectopic or eutopic endometrial epithelium. *ARID1A* mutations are associated with loss of ARID1A expression as shown in an example of uterine endometrioid carcinoma while normal endometrium expresses ARID1A protein.

agent.[76,77] During differentiation, ARID1A-containing BAF complexes directly targeted and repressed several E2F-responsive promoters, as well as the c-myc promoter, whose repression is critical for induction of p21 in this cellular model.[76,77] Using the same cell model, Nagl et al. discovered that ARID1A- and ARID1B-containing BAF complexes had opposite effects on cell-cycle regulation. Cell cycle arrest induced by serum deprivation was dependent on ARID1A activity, whereas re-entry into cell cycle after serum stimulation required ARID1B.[14] In general, ARID1A is required for proper cell cycle arrest at the G_1 checkpoint in response to various cellular signals and environmental cues.

In an ovarian cell line model, physical interactions among p53, ARID1A, and BRG1 were observed, and both p53 and BRG1 co-occupied the promoters of *CDKN1A* (p21) and *SMAD3*.[17] Silencing of ARID1A reduced the occupation of BRG1 at the promoters of *CDKN1A* and *SMAD3*, and reduced their transcriptional activity. Moreover, p53 was required for ARID1A-induced p21 expression. This evidence suggests that ARID1A-containing SWI/SNF complexes are recruited to the *CDKN1A* promoter through interaction with p53, leading to induction of p21 and subsequent cell cycle arrest.

ARID1A as a Caretaker

ARID1A, in addition to its role as a "gatekeeper", may also function as a "caretaker", a tumor suppressor that maintains the genomic stability by preventing sequence mutations and structural aberrations in chromosomes. In its caretaker function, ARID1A participates in mediating DNA decatenation, and probably, in facilitating DNA damage repair and mismatch repair.

Like BRCA1, ARID1A physically interacts with topoisomerase IIα (TOP2A), which decatenates newly replicated sister chromatids, ensuring proper chromosome segregation during mitosis.[78,79] TOP2A chromatin binding depends on its interaction with ARID1A and the ATPase activity of SWI/SNF complexes. ARID1A knockdown, similar to Brg1 deletion and BRCA1 deficiency, phenocopies TOP2A inhibition. Failure to resolve catenated DNA by TOP2A leads to increased anaphase bridge formation during mitosis, resulting in aneuploidy as well as polyploidy.[79] If this in vitro finding can be extrapolated to human tissues, one would expect to observe that tumors harboring *ARID1A* mutations are characterized by an increase in chromosomal instability or manifested by frequent anaphase bridge. Further studies are required to confirm the biological significance of the above finding.

SWI/SNF complexes have been shown to facilitate repair of DNA damage. SWI/SNF is recruited to DNA double strand breaks (DSB) by interacting with acetylated H3 in gamma-H2AX-containing nucleosomes,[80] and promotes ATM-mediated phosphorylation of H2AX around DSB,[81] forming a positive feedback loop that facilitates DSB repair. SWI/SNF is also involved in nucleotide excision repair, mediating the repair of UV-induced pyrimidine dimers[82,83] and chemical-induced crosslinking of DNA.[84] BRG1 interacts with BRCA1[85]

and facilitates BRCA1 recruitment to DNA damage sites.[86] Dysfunctional SWI/SNF, therefore, may compromise DNA damage repair and subsequently promote genomic instability. Although the extent to which ARID1A is involved in SWI/SNF-mediated DNA damage repair remains to be determined, given the high frequency of *ARID1A* mutation in a broad spectrum of cancers, it is likely that ARID1A plays a critical role in this process.

Defects in mismatch repair (MMR) caused by mutation or promoter hypermethylation of MMR genes are prevalent in colorectal, gastric, and endometrial cancers.[87] MMR deficiency is responsible for slippage errors during DNA synthesis, resulting in microsatellite instability (MSI) involving short repeats of mono- or oligonucleotides. MSI thus represents the phenotype of MMR deficiency and is associated with a remarkably elevated rate of sequence mutations in cancer cells. *ARID1A* mutation has been associated with MSI in gastric and colorectal cancers.[43,47] Similarly, loss of ARID1A protein expression is associated with loss of expression of mismatch repair proteins and/or MSI in gastric carcinoma[46] and uterine endometrioid carcinoma.[88,89] However, controversy remains as to whether loss of ARID1A is the cause or result of MMR deficiency. The *ARID1A* gene contains numerous short mononucleotide repeats that can be affected by slippage errors during DNA replication resulting from a mismatch repair defect. Wang et al. suggested that *ARID1A* mutation was the result rather than cause of mismatch repair defects because most (89%, 25/28) of the *ARID1A* mutations found in MSI gastric cancers were indels involving short mononucleotide repeats; whereas, similar indels only occurred in 1 of 17 *ARID1A* mutations in microsatellite stable gastric cancer.[43] Similarly, in a study by Jones et al.,[44] *ARID1A* indels involving short mononucleotide repeats were identified in 10 of 11 (91%) colorectal and gastric cancers with MSI but only 2 of 8 (25%) microsatellite stable ones. Cajuso et al. found a high prevalence (18/46, 39%) of *ARID1A* mutations in MSI colorectal cancer, with 17 of 25 (68%) mutations (from 18 tumors) representing frameshifts involving mononucleotide repeats.[90] Hence, the high frequency of *ARID1A* mutations in gastrointestinal cancers with MSI is likely the consequence of MMR defects. A similar *ARID1A* mutation spectrum, however, is not observed in uterine endometrioid carcinoma with MSI, as none of the 26 *ARID1A* somatic mutations in MSI endometrioid carcinoma in a TCGA study are indels involving short mononucleotide repeats.[32] Since the patterns of *ARID1A* mutations in MSI samples are quite different between endometrial and gastrointestinal cancers, it is possible that the causal relationship between *ARID1A* mutations and mismatch repair depends on tissue origins. In support of this view, Tjalling Bosse et al. found that ARID1A loss was significantly more prevalent in uterine endometrioid carcinomas with sporadic MSI as compared with uterine endometrioid carcinomas from patients with Lynch syndrome, a germline defect of MMR genes.[89] This also suggests that *ARID1A* mutation is unlikely the consequence of mismatch repair defects in uterine endometrioid carcinoma.

ARID1A and Epstein–Barr Virus

ARID1A mutation or loss of its expression has been found to be associated with Epstein–Barr virus (EBV)-associated gastric cancers.[46] Wang et al. found *ARID1A* mutation in 47% of EBV-infected, microsatellite stable gastric cancer samples, which was substantially higher than in microsatellite stable gastric cancers without EBV infection (10%).[43] Abe et al. observed that loss of ARID1A expression was prevalent in EBV-associated (34%) and MLH1-lost (29%) gastric cancer, but rare in gastric cancer without EBV infection and MLH1 loss (5%).[46] Histologically, EBV-associated gastric cancer is characterized by an intense infiltrate of lymphocytes within tumors,[91] which is also a histological feature of colorectal and gastric cancers with MSI.[92,93] Interestingly, an RNAi screen revealed that knockdown of ARID1A rendered Jurkat leukemia cells resistant to Fas (CD95)-mediated apoptosis,[94] a killing mechanism used by T cells and NK cells.[95] The association between *ARID1A* mutation and cancer subtypes rich in lymphocytic infiltration raised the speculation that *ARID1A* mutation may equip cancer cells to escape from immune surveillance. Elucidation of the role played by ARID1A in immune evasion may provide insights germane to approaches using immunotherapy.

Pathway Crosstalk

The observation that mutations in different cancer genes frequently co-occur suggests that these mutations may cooperate in tumor development. On the other hand, the occurrence of mutual exclusion of mutations between two different cancer genes suggests that these mutations may have similar effects or may act within the same functional pathway. Correlation of mutation status of different genes has discovered several pathways that potentially cooperate with ARID1A.

Collaboration between ARID1A Mutation and PI3K/Akt Pathway Activation

Accumulating evidence suggests that *ARID1A* mutation may cooperate with the PI3K/Akt pathway to promote development of cancer, especially ovarian endometriosis-associated cancers. In ovarian clear cell carcinoma, *ARID1A* mutation or loss of protein expression often co-occurs with *PIK3CA* mutation.[23,26,71] Combining the data from Jones et al., Yamamoto et al. and Huang et al., *ARID1A* was found to be mutated or lost in 41 (72%) of 57 ovarian clear cell carcinomas with *PIK3CA* mutation but in only 41 (43%) of 95 tumors without PIK3CA mutation ($P = 0.0007$, **Fig. 2A**).[23,26,71] In addition, Huang et al. also found that ARID1A was more frequently lost in tumors with *ZNF217* amplification,[26] a potential oncogene that was shown to augment the PI3K/Akt signaling activity by upregulating ErbB3 expression.[96] In ovarian endometrioid carcinoma, *ARID1A* was

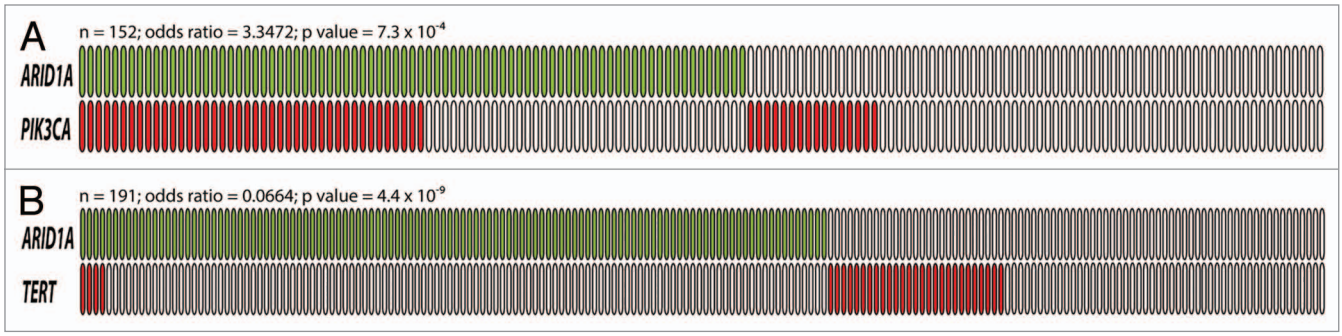

Figure 2. The relationship between *ARID1A* mutation and *PIK3CA* mutation (**A**), and between *ARID1A* mutation and *TERT* promoter mutation (**B**). Green boxes are tumors harboring somatic *ARID1A* mutations while red boxes are tumors with either *PIK3CA* mutation or *TERT* promoter mutation. Each box represents an individual tumor. The total number of tumors, the odds ratio (OR) and *P* values are shown above each diagram.

mutated in 80% (4/5) of ovarian endometrioid carcinoma with *PTEN* mutation but in only 20% (5/25) of samples without *PTEN* mutation ($P = 0.0195$).[97] In addition to gynecologic cancers, *ARID1A* mutations were also significantly associated with *PIK3CA*-activating mutations in gastric carcinomas.[45] Viewing the totality of the evidence, it is likely that loss of ARID1A function and dysregulation of the PI3K/Akt signaling pathway have a synergistic effect on tumor development.

The Potential Roles of ARID1A in p53 and Telomere Biology

An inverse relationship between *ARID1A* and *TP53* mutations has been observed in uterine endometrioid carcinoma,[88,89] gastric carcinoma,[43,45] and esophageal dysplasia/adenocarcinoma.[41] ARID1A has been shown to directly interact with p53 and to modulate p53-mediated transcriptional regulation in ovarian cancer.[17] This suggests that ARID1A and p53 suppress tumor development in a codependent fashion; therefore, loss of ARID1A may have a similar effect as p53 deficiency. In addition to TP53, Wu et al. have recently discovered a tendency toward mutual exclusivity between ARID1A loss and *TERT* promoter mutation in ovarian clear cell carcinoma,[98] suggesting that ARID1A may also play a role in telomere biology (**Fig. 2B**).

Potential Synthetic Lethality with *ARID1A* Mutation

A recent systematic screening of genetic vulnerability across cancer cell lines identified *ARID1B* as the top gene required for survival of cancer cells with inactivating *ARID1A* mutations.[99] ARID1B, a subunit of SWI/SNF complex mutually exclusive with ARID1A, was required for stable assembly of the SWI/SNF complex in ARID1A-deficient cells. Silencing ARID1B impaired cellular proliferation in cancer cells with *ARID1A* mutations but not in cells with wild-type *ARID1A*. This result suggests that ARID1B is a potential therapeutic target for cancers with *ARID1A* mutation.

ARID1A as a Prognostic Predictor

The prognostic significance of *ARID1A* mutation or loss of expression has been evaluated in ovarian, endometrial, cervical, urinary bladder, breast, and gastric cancers. These studies have revealed that in different tumor types ARID1A alterations have a different prognostic impact. In ovarian clear cell carcinoma, no significant differences in survival between ARID1A-negative and ARID1A-positive cases were observed in four different studies.[25,27,28,37] In endometrial cancer, no association between ARID1A loss and disease-specific survival was observed in three studies on endometrioid carcinoma,[34,35,88] or in one study on clear cell carcinoma.[37] In cervical cancer, ARID1A loss was a predictor of reduced overall survival in one study,[39] but not in another.[38] In bladder transitional cell carcinoma, Gui et al. found no association between *ARID1A* mutation status and tumor grade or stage.[58] In breast cancer, low ARID1A mRNA expression has been associated with aggressive features, including higher grade, higher stage, hormone receptor negativity, and ERBB2 positivity,[55,56,69] although low ARID1A is not an independent prognosticator for disease-specific survival.[55,56] In clear cell renal cell carcinoma, lower protein and mRNA expression levels were associated with worse prognosis.[70] In gastric cancer, ARID1A loss was found to be an independent predictor for better prognosis in one study,[43] but worse prognosis in another.[75] These conflicting results may be due to the fact that the multivariate analyses employed did not incorporate both MSI and EBV infection, two critical confounding factors that are correlated with ARID1A loss and associated with better prognosis.[100,101] Taking both MSI and EBV infection into account, Abe et al. showed that ARID1A loss was associated with poor prognosis only in gastric cancers without MSI and EBV infection.[46]

Conclusion

Recent cancer genome studies have established ARID1A as an important tumor suppressor, whose mechanisms in tumor suppression and interplay with other oncogenic pathways have just

begun to be unraveled. Although tumor suppressor genes inherently present challenges for developing targeted therapeutics, this obstacle will likely be circumvented by addressing the following issues. First, the involvement of ARID1A in maintaining genomic stability makes tumors with *ARID1A* mutations potential candidates for therapeutics based on synthetic lethality—an ARID1A-deficient tumor, with genomic instability as its Achilles' heel, may be vulnerable to therapies targeting certain pathways involving genome maintenance. Alternatively, ARID1B presents as a new promising therapeutic target for synthetic lethality in cancers with *ARID1A* mutation and warrants further investigation. Furthermore, with more epigenetic therapies emerging in cancer medicine,[102] it is of paramount importance to delineate the landscape of ARID1A-containing SWI/SNF targets and the epigenetic alterations that follow *ARID1A* mutation. This analysis will serve as a springboard for future development of epigenetic therapeutics. Last but not least, due to the possible interaction between *ARID1A* mutation and the PI3K pathway, it is interesting to investigate the effect of PI3K inhibitors on tumors with different *ARID1A* mutation status. This will provide new opportunity to fine-tune personalized medicine using PI3K inhibitor. Addressing these issues will likely yield fruitful results, leading to the application of personalized medicine to ARID1A deficient tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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